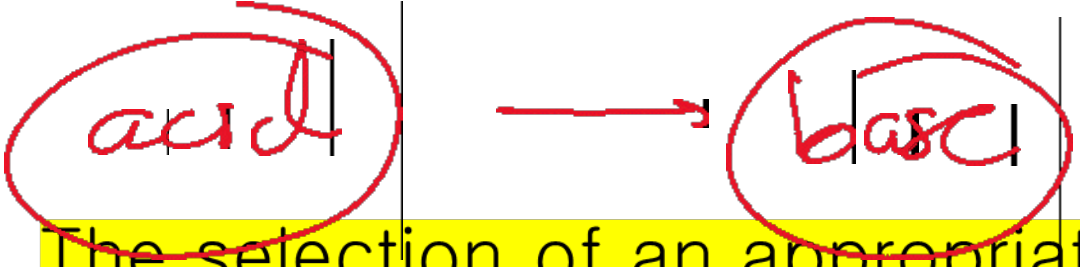
Salt Selection in Drug Development

Adapted from *Pharmaceutical Technology,* **2008**, *32(3)*, 128.



The selection of an appropriate salt form for a potential drug candidate is an opportunity to modulate its characteristics to improve bioavailability, stability, manufacturability, and patient compliance

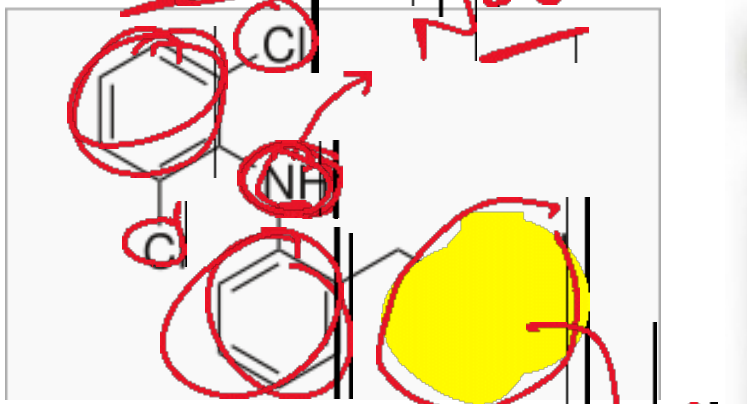
Sometimes the pharmacokinetics property is not optimum so we can modify it and make it optimum by making it salt.

Example: most drugs in the market are water insoluble so you can increase water solubility by make it salt. So, increase oral absorption.

Increase solubility is not the only benefits obtained from making salts, we have other benefits

Example of drugs available as salts

Diclofenac is acidic, because of COOH, so we need to make salt with base. (Na, K, Diethylamine)

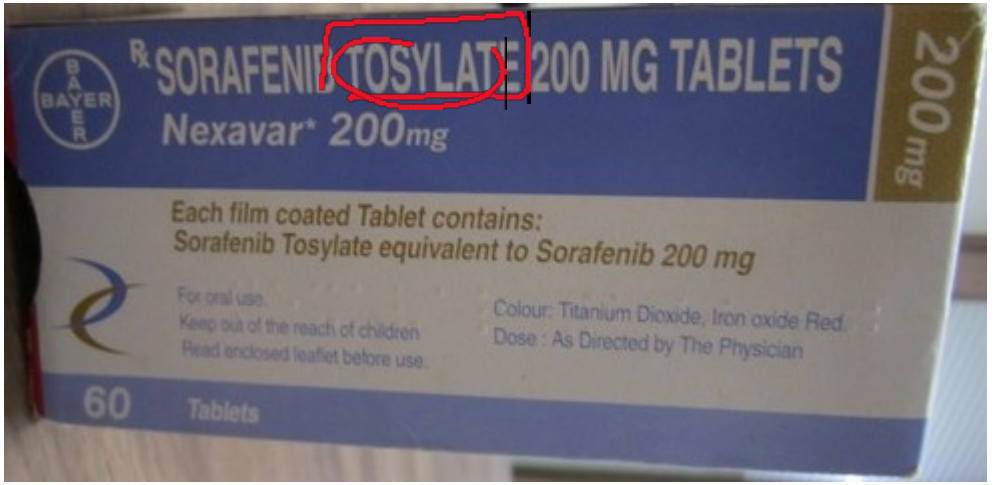


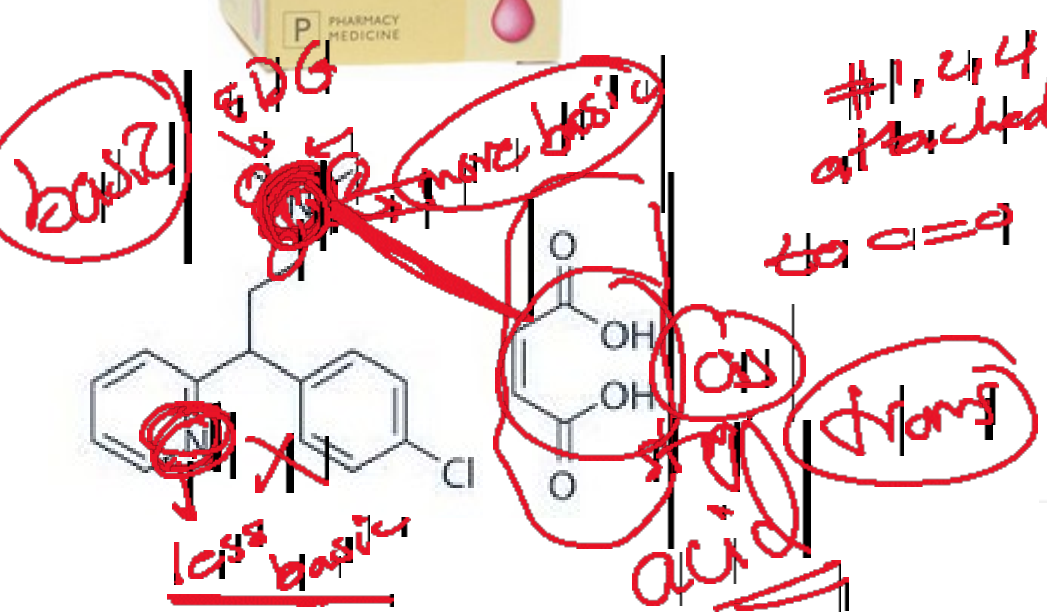
Chlorphenamine is basic react it with acid to make salt, it is a salt with maleic acid

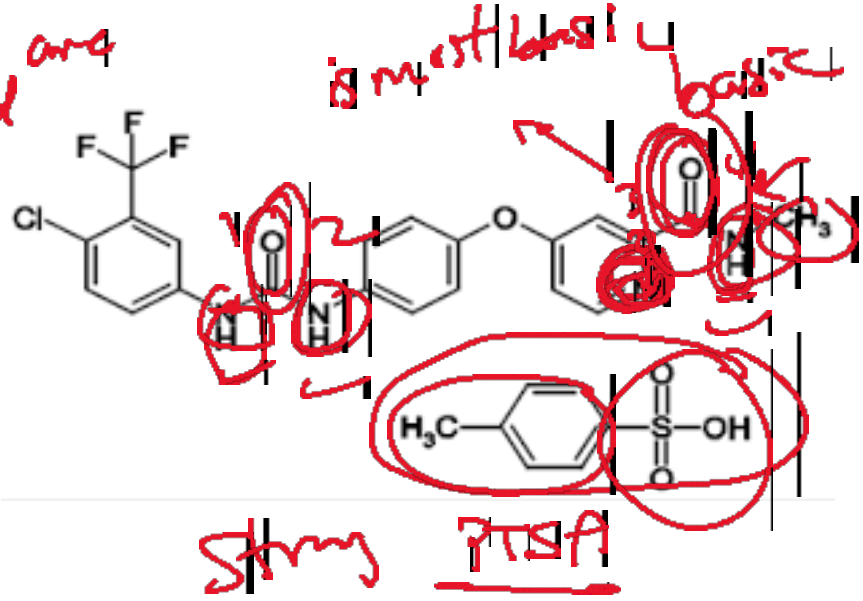
The cis of this structure acid is maleic acid, but the same acid of trans is Fumaric acid

Sorafenib is kinase inhibitor for cancer, it is a basic drug react with acid PTSA

ALMUS
Chlorphenamine Maleate 2mg/5ml
Oral solution
Hayfever and allergy relief
Fast and effective relief from itchiness, redness and swelling caused by skin allergies and hayfever.
SUGAR AND COLOUR FREE
150ml
P PHARMACY MEDICINE


BAYER
SORAFENIB TOSYLATE 200 MG TABLETS
Nexavar* 200mg
200 mg
Each film coated Tablet contains:
Sorafenib Tosylate equivalent to Sorafenib 200 mg
For oral use.
Keep out of the reach of children
Read enclosed leaflet before use.
Colour: Titanium Dioxide, Iron oxide Red.
Dose : As Directed by The Physician
60 Tablets





Introduction

- An estimated 50% of all drug molecules used in medicinal therapy are administered as salts.
- This fact indicates that the salification, or salt formation, of a drug substance is a critical step in drug development.
- A drug substance often has certain suboptimal physicochemical or biopharmaceutical properties that can be overcome by pairing a basic or acidic drug molecule with a counterion to create a salt version of the drug.
- The process is a simple way to modify the properties of a drug with ionizable functional groups to overcome undesirable features of the parent drug.

Diagrammatic representation of salt formation

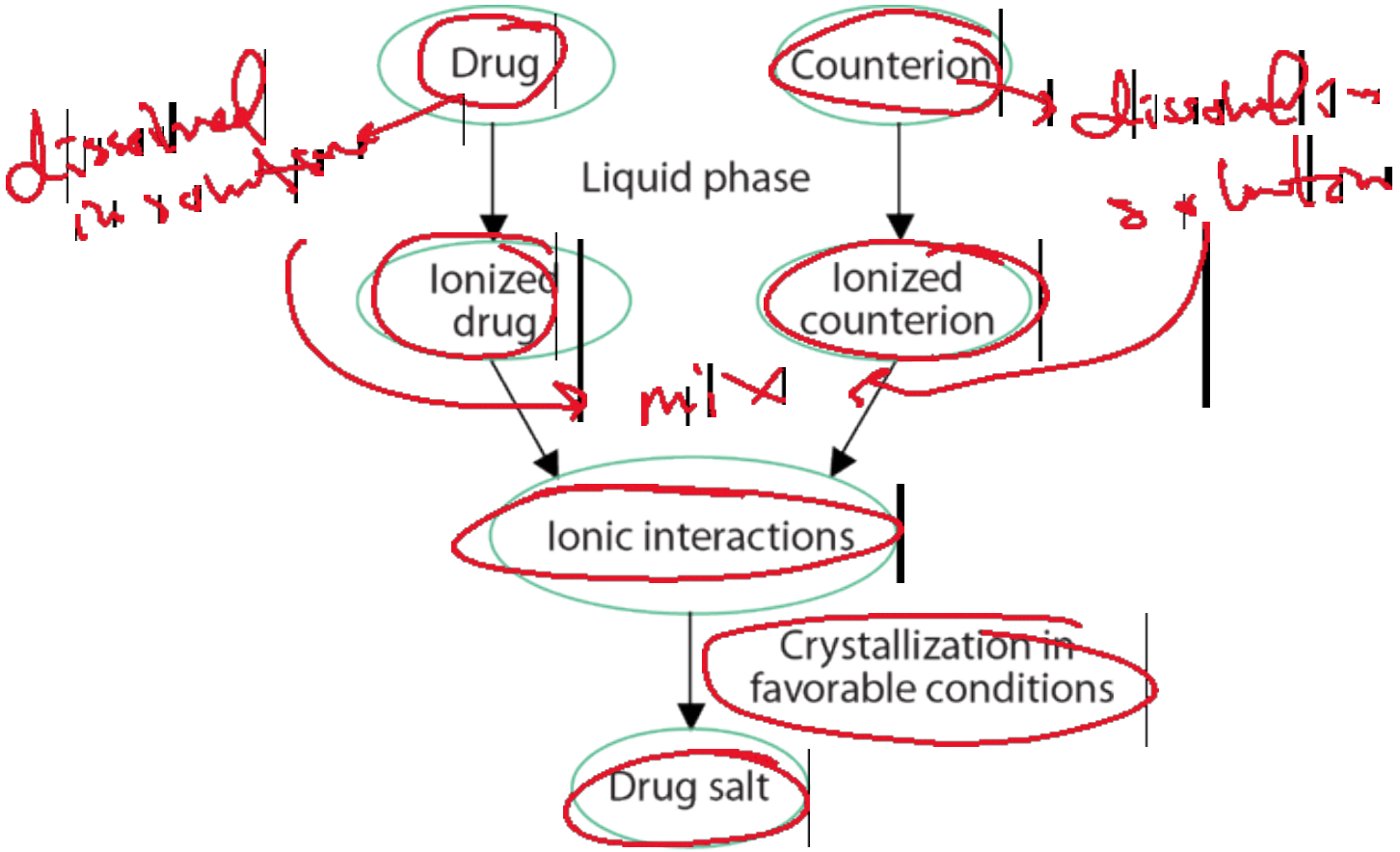


Table Ia: Advantages of salt formation for drug properties.

Advantage of salt formation	Reference
or dissolution rate of drugs	(8, 9)
	(9)
Targeted drug delivery of dosage form	(10, 11)
	(6, 12)
	(12)
Improved photostability	(13)
	(2, 14)
Improved permeability	(6, 9)
(e.g., taste acceptability)	(2)
Improved drug efficacy [The pharmacological actions of counterions can mitigate side effects. For example, dimenhydrinate (salt of diphenhydramine with 8-chloro theophylline) reduces the soporific effect of diphenhydramine (antihistaminic) because theophylline acts as a stimulant.]	(15)
Reduced pain of injection (e.g., the morpholine, diethylamine, and *N*-methyl glucamine salts of cephalosporins)	(6)
, resulting in improved milling and new formulation opportunities (e.g., topical application forms and soft gelatin capsules)	(9, 16)
Ease of purification, handling, or processability	(2, 17)
Improved compactibility	(18)
Extended patent protection	(1, 19)
Absolute configuration of chiral drugs through single-crystal X-ray diffraction. Racemic resolution of diastereomeric salts and rotamers	(20)

Separation of stereoisomers

Table Ib: Disadvantages of salt formation for drug properties.

	Reference
[illegible] percentage of active content of drug [illegible]te in the formulation: • Inactive counterions generally represent 20–50% of the weight of the drug substance • Increased powder volume causes problems for tableting and capsule filling (the tablet or capsule must be small enough to be easily swallowed) or patient compliance	(21)
[illegible] formation of [illegible] resulting in greater variability of the drug's pharmaceutical properties	(21, 22)
[illegible]ty for hydrochloride salts in gastric fluid resulting from precipitated free acid or base at the surface of the solid dosage form	(23)
[illegible] solid-state [illegible] of the salt	(23)
[illegible] (e.g., highly acidic hydrochloride salts damage punch tooling)	(9)
Possible disproportionation (dissociation) of hydrochloride or hydrobromide, resulting in the release of hydrohalide gas or reaction with excipients or process-related chemicals	(6)
[illegible]	(24)

Solution: water soluble salts
Suspension: water insoluble salts

Table II: … forms based on intended pharmaceutical profile.

	Example
	Depending upon the type of dosage form required (1): • Solid oral dosage forms—hydrochlorides and maleates • … or injectables—hydrochlorides and mesylates • …—salts with … such as embonate, estolate, and tosylate • Suppositories—free base
	Fo… The … ons such as tosylate may …
… desired bioavailability	• …—hydrochloride and sodium • …—salts with … … s such as embonate, estolate, and tosylate (1)
	…
	• The … implications. • Counterions with known or potentially undesirable … are … • Maleic acid (Pravadoline maleate) causes renal tubular lesions in dogs (31). • Certain mesylate salts may be genotoxic (32).
	The unauthorized commercial use of patented salt forms is restricted.
Marketing preferences	Omeprazole, which was originally marketed in a capsule, was formulated as a tablet after it was linked with magnesium salt (omeprazole magnesium) (33).

Why don't we make salt with Lithium?
Bec. Of toxicity

Table III: Salt forms in *USP* 2006.

Anionic salt form	Percentage*	Anionic salt form	Percentage*
Acetate	2.59 (6.70)	Malate	0.08 (0.22)
Benzoate	0.33 (0.86)	Maleate	1.42 (3.67)
Besylate	0.17 (0.43)	Mandelate	0.08 (0.22)
Bitartrate	0.59 (1.51)	Mesylate	1.00 (2.59)
Bromide	0.59 (1.51)	Methyl bromide	0.08 (0.22)
Carbonate	0.42 (1.08)	Methyl sulfate	0.08 (0.22)
Chloride	1.76 (4.54)	Mucate	0.08 (0.22)
Citrate	1.17 (3.02)	Napsylate	0.08 (0.22)
Edetate	0.17 (0.43)	Nitrate	0.92 (2.38)
Edisylate	0.08 (0.22)	Pamoate (embonate)	0.25 (0.65)
Estolate	0.08 (0.22)	Phosphate and diphosphate	1.92 (4.97)
Fumarate	0.50 (1.30)	Salicylate and disalicylate	0.67 (1.73)
Gluceptate	0.17 (0.43)	Stearate	0.08 (0.22)
Gluconate	0.67 (1.73)	Succinate	0.92 (2.38)
Hydrobromide	0.42 (1.08)	Sulfate	4.10 (10.58)
Hydrochloride	15.48 (39.96)	Tartrate	0.84 (2.16)
Iodide	0.33 (0.86)	Tosylate	0.08 (0.22)
Lactate	0.08 (0.22)	Triethiodide	0.08 (0.22)
Lactobionate	0.08 (0.22)	Valerate	0.25 (0.65)
Cationic salt form	**Percentage**	**Cationic salt form**	**Percentage**
Aluminum	0.67 (4.65)	Meglumine	0.33 (2.33)
Benzathine	0.33 (2.33)	Potassium	1.59 (11.05)
Calcium	1.26 (8.72)	Procaine	0.08 (0.58)
Ethylene diamine	0.08 (0.58)	Sodium	9.04 (62.79)
Lysine	0.17 (1.16)	Tromethamine	0.25 (1.74)
Magnesium	0.25 (1.74)	Zinc	0.33 (2.33)
Other salts	3.01		
No salt	43.85		

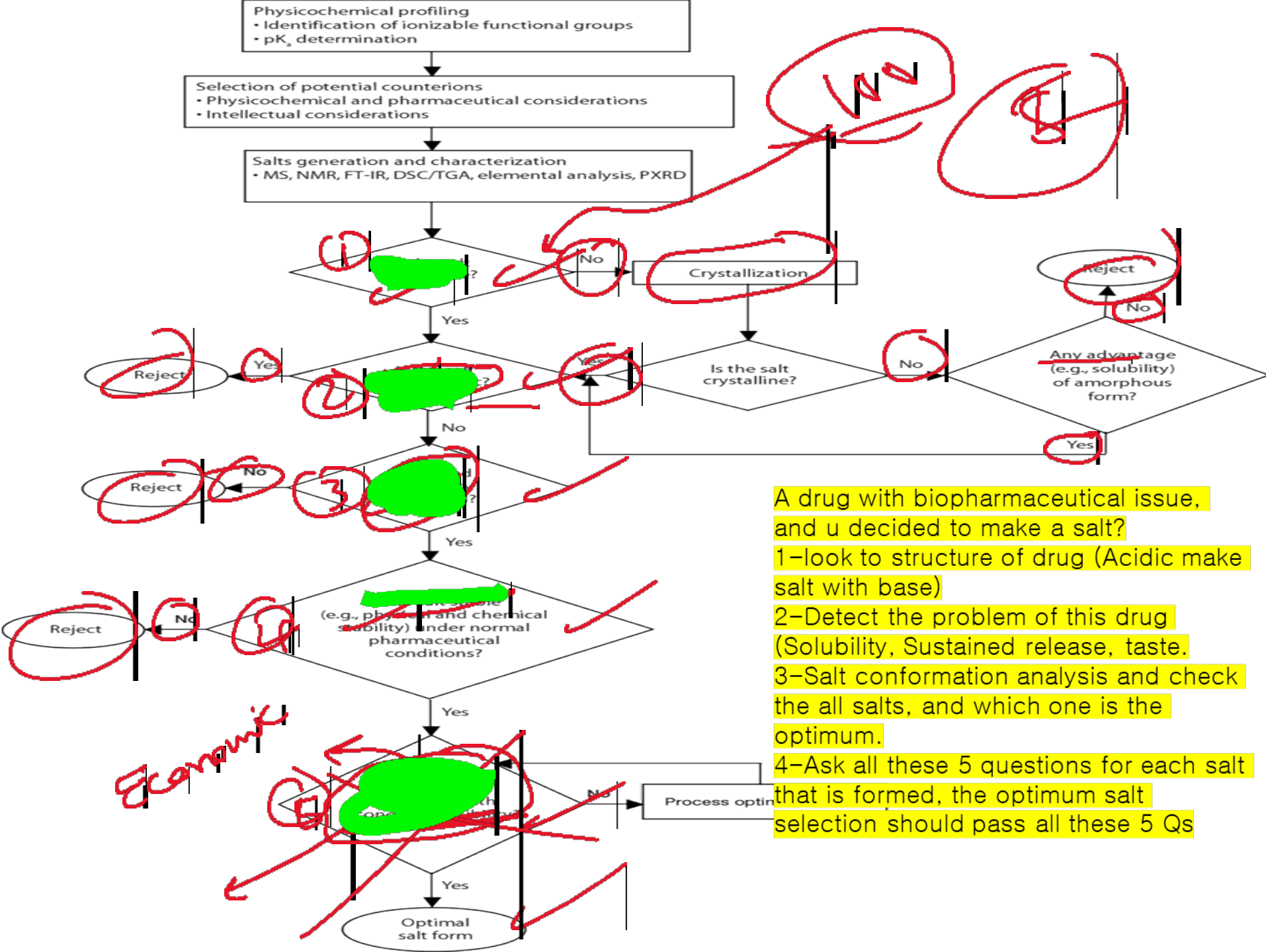
*The first figure given is the percentage of salt form as a function of all medicinal compounds. The figure in parentheses is the percentage of anionic or cationic salt form as a function of the total number of anionic or cationic drugs, respectively.

Techniques for salt conformation, to differentiate between salts and parent drug

What are the differences?
1-Solubility
2-Melting point
3-NMR
4-Diffraction pattern

Table IV: Techniques for the characterization of salt forms.

Technique	Information derived
[illegible]	Salt formation, stoichiometry
Optical-polarized microscopy	Crystallinity, particle morphology, polymorphs
Hot-stage microscopy	Thermal behavior, polymorphic transitions
Scanning electron microscopy	Particle morphology
[illegible]	Phase purity, characteristic peak patterns
Variable-temperature PXRD	Thermal stability
Single-crystal PXRD	Polymorphic structure, basic crystallographic information (e.g., unit cell, molecular packing, bond length, angles)
Fourier transform infrared spectroscopy (FTIR)	Salt formation (characteristic peak shifts), stoichiometry
Thermal FTIR	Molecular changes with temperature, thermal stability
Differential scanning calorimetry (DSC)	Melting point, polymorphism, phase purity, solid-state stability
Thermogravimetric analysis (TGA)	Volatile content, polymorphism, solid-state stability (degradation pattern of salts, desolvation kinetics)
Intrinsic dissolution rate	Dissolution rate irrespective of particle size, polymorphic changes
Saturated salt solutions	Hygroscopicity at different relative humidities during handling, transportation, and use
Dynamic vapor sorption apparatus	Hygroscopicity, hysteresis effects
Raman spectroscopy	Salt formation (e.g., characteristic peak shifts), polymorphs
Variable-temperature Raman	Molecular changes with temperature, thermal stability, polymorphic transitions
Thermogravimetry–mass spectrometry (TG-MS)	Elaboration of degradation mechanism, identification of solvates
Thermogravimetry–infrared spectroscopy (TG–IR)	Thermal decomposition, kinetics of decomposition, identification of volatile components or solvates
High-performance liquid chromatography	Salt formation, stoichiometry, purity
Nuclear magnetic resonance spectroscopy (NMR)	Salt formation, stoichiometry, purity
Solid-state NMR	Phase purity, molecular mobility, type of polymorphism
Isothermal microcalorimetry	Solid-state stability, excipient compatibility study



A drug with biopharmaceutical issue, and u decided to make a salt?

1-look to structure of drug (Acidic make salt with base)

2-Detect the problem of this drug (Solubility, Sustained release, taste.

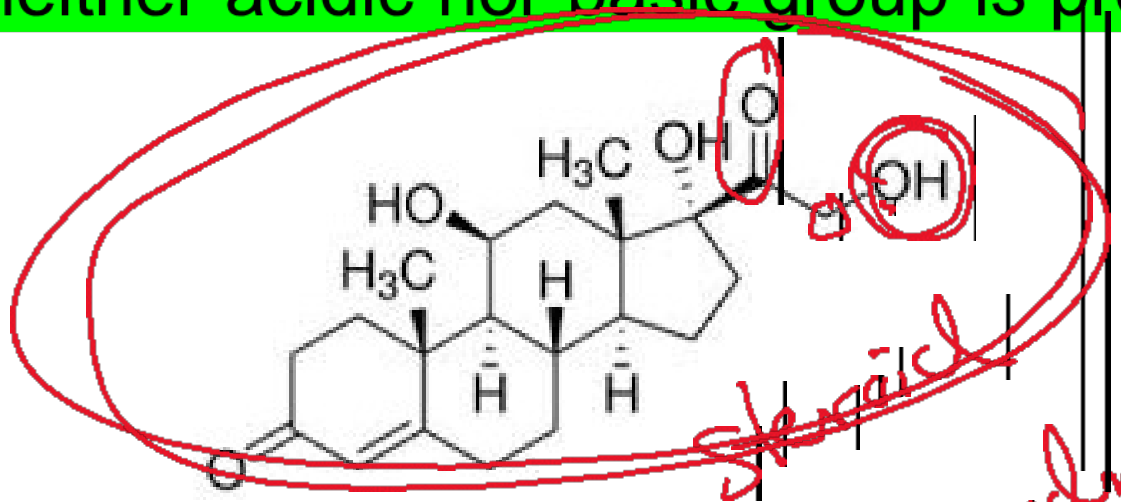
3-Salt conformation analysis and check the all salts, and which one is the optimum.

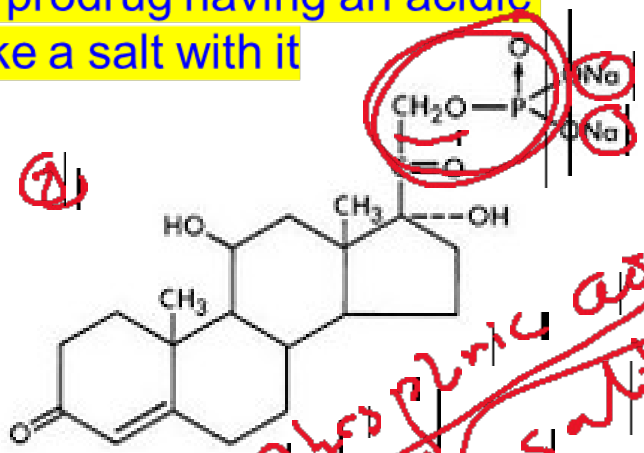
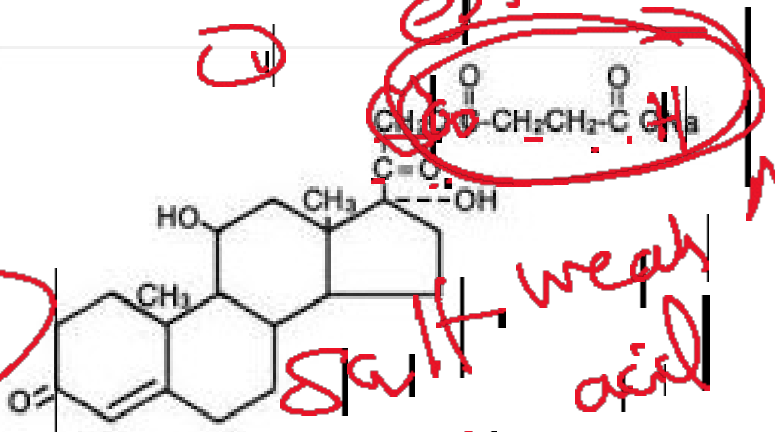
4-Ask all these 5 questions for each salt that is formed, the optimum salt selection should pass all these 5 Qs

Conclusion

- Selecting an optimal salt form for development is a critical step in ensuring the efficient and successful development of a robust product.
- Salt selection requires a well designed screening strategy that fulfills the essential and desirable criteria that set the standard for salt screening.
- In addition, salt selection procedures must also assess the regulatory, intellectual, and marketing considerations to balance the drug's physicochemical and biopharmaceutical properties against commercial considerations. (improve the drug property but should not be too much expensive)

If neither acidic nor basic group is present?



Solution: water-soluble prodrugs not salts

I will make a prodrug having an acidic group to make a salt with it